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Adoptive cell transfer: New technique could make cell-based immune therapies for cancer safer, more effective

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A team led by Michel Sadelain, MD, PhD, Director of the Center for Cell Engineering at Memorial Sloan-Kettering Cancer Center, has shown for the first time the effectiveness of a new technique that could allow the development of more-specific, cell-based immune therapies for cancer. Their findings were reported online today in *Nature Biotechnology*.

Immunotherapies—which make use of patients' own immune cells that have been augmented in the laboratory—have shown some early success in the treatment of blood cancers including certain types of leukemia. For most cancers, however, cell-based therapies have been harder to develop, in large part because it has been difficult for investigators to train immune cells to specifically attack cancer cells without damaging normal, healthy cells in the body.

The treatment approach, known as adoptive cell transfer (ACT), involves engineering an immune cell called a T cell. In the ACT process, T cells are removed from a patient and a gene is added to allow the T cells to recognize a certain antigen on the surface of a cancer cell. The enhanced cells are grown in the laboratory and then infused back into the patient to seek out and attack cancer cells.

"We are getting better at working with these T cells and enhancing them so that we can get a powerful immunological response against cancer,"

Dr. Sadelain says. "The dilemma now is that we are concerned with limiting these responses and making them as targeted as possible to avoid potentially harmful side effects."

Cancer cells overproduce certain antigens, which can help T cells to recognize them, but those same antigens are often found in lower levels on healthy cells. "There are very few antigens, if any, that are found only on cancer cells," Dr. Sadelain explains.

"Now we are bringing in a completely new concept," he adds. "If there is no single unique antigen that is found on the surface of the cancer cell we want to target, we instead create T cells that recognize two different antigens found on the tumor cell—a signature that will be unique to that type of cancer—and only attack cells with both antigens, sparing the normal cells that express either antigen alone."

The new technique makes use of receptors known as chimeric antigen receptors (CARs), which allow T cells to target antigens on the surface of a tumor cell, coupled with another type of receptor called a chimeric costimulatory receptor (CCR), by which the T cells can recognize a second antigen.

The CAR and the CCR work together through a process known as balanced signaling, in which the presence of either antigen on its own is not enough to trigger the immune response. Only tumor cells that carry both antigens will be targeted.

In the Nature Biotechnology study, the team created T cells that carried a CAR for an antigen called PSMA and a CCR for an antigen called PSCA. Both PSMA and PSCA are found on prostate cancer cells. The investigators then generated mouse models of prostate cancer and infused the mice with the engineered cells. They found that the T cells attacked only tumors that carried antigens for both PSMA and PSCA.

"We are the first to test this concept and show that it works," Dr. Sadelain concludes. "We plan to develop clinical trials based on this approach, although we have not yet decided whether the first study will be a trial for prostate cancer or for a different type of cancer using two other antigens. Ultimately, our goal is to create targeted immunotherapies that are both potent and safe for patients."

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